REMARKS

Applicant's remarks, which are submitted herewith, supplement and do not replace those submitted on March 25, 2004 in response to the Examiner's Final Office Action of September 25, 2003.

Claims 1, 3, 5, 10, 11, and 19 have been amended. Claims 2, 4, 9 and 13-16 have been cancelled without prejudice or disclaimer to pursue this subject matter in continuation or divisional applications. New claims 24-41 have been added. Upon entry of the foregoing amendment, claims 1, 3, 5-8, 10-12, 17-19 and 21-41 will be pending.

Applicants respectfully submit that no prohibited new matter has been introduced by the amendments. Written description support for the new claims can be found throughout the specification. For example, support for "identifying a subject suffering from an inflammatory condition" can be found throughout the specification, but specifically on pages 8-20 and original claim 1. Support for "identifying a subject suffering from allergic blepharoconjunctivitis" can be found on page 15 and original claim 10. Support for "identifying a subject suffering from classic type 1 hypersensitivity" can be found on pages 11 and 12 and original claim 11. Support for "blocking nerve and mast cell release of preformed mediators that produce vasodilation and permeability, altered sensory experience, edema and/or erythema" can be found on page 4, lines 16-18. Support for "but below that necessary to cause substantial muscle weakness can be found in claim 2, as originally filed. Claims 24-26 and 27-29 are based on pending claims 17-19 and 21-23. Support for "the dose of botulinum toxin is between 2 and 60 botulinum units" can be found on page 2 (lines 2 and 3) and, for example, lines 3 and 4 of the abstract. Support for "the dose of botulinum toxin is between 0.5 and 5.0 botulinum units" can be found on page 4 (line 10). Support for "therapeutically effective dose" can be found in original claim 4 and throughout the specification.

Interview Summary

Applicant thanks the Examiner for the courtesy of an interview. Einar Stole (Applicant's representative), Gary E. Borodic (inventor), and Gerald Ewoldt (Examiner)

were present at the interview which was held on May 17, 2004 at the United States Patent and Trademark Office.

During the interview Dr. Borodic described the concept of inflammation, and identified elements of the inflammatory cascade. Specifically, Dr. Borodic described how neurogenic inflammation is an inflammatory cascade that originates with stimulation or injury to a nerve cell that results in the release of pre-formed inflammatory mediators, which in turn produce the release of other inflammatory mediators—thereby producing a cascade—from a variety of cells and tissues, including mast cells. Dr. Borodic identified five (5) scientific publications that describe the involvement and role of mast cells in neurogenic inflammation. These publications are submitted herewith in the attached Information Disclosure Statement.

Enablement

In the Final Office Action of September 25, 2003, the Examiner rejected claims 2-4 under 35 U.S.C. § 112, first paragraph, for purportedly not enabling the claimed invention. Applicant traversed this rejection in the response filed on March 25, 2004. The following remarks are made to supplement that traversal.

Claim 4, which is drawn to a method of reducing inflammation comprising an effective dose of botulinum toxin less than 2.5 botulinum units, has been cancelled. Thus, with respect to claim 4, this rejection is moot. With respect to newly added claims 34-41, these claims recite a dose range from 2 to 60 botulinum units or from 0.5 to 5.0 botulinum units, support for which is found throughout the specification (page 2 (lines 2 and 3) and, for example, lines 3 and 4 of the abstract; page 4 (line 10)).

In view of the foregoing amendment and remarks, Applicant respectfully requests withdrawal of the outstanding enablement rejection to the extent it may be applied to new claims 34-41.

Written Description

In the Final Office Action of September 25, 2003, the Examiner rejected claims 17-19 and 21-23 under 35 U.S.C. § 112, first paragraph, for purportedly not providing an

adequate written description of the claimed invention. The Examiner also denied benefit of priority to U.S. Provisional Application Serial No. 60/097,846 because the specification purportedly does not provide written description support for a method for treating neurogenic inflammation. Applicant traversed this rejection in the response filed on March 25, 2004. The following remarks are made to supplement that traversal.

Applicant has previously provided numerous references to the specification of the above-identified application, including the Declaration of Martin Acquadro, that demonstrate that the specification provides a written description for methods of treating neurogenic inflammation using botulinum toxin. In addition, Applicant respectfully submits that neurogenic inflammation is central to the disclosure of the above-identified application for several reasons. First, neurogenic inflammation is an inflammatory cascade that originates with stimulation or injury to a nerve cell that results in the release of pre-formed inflammatory mediators. Webster's Dictionary (The Rosetta Edition) defines neurogenic inflammation as:

> "Inflammation caused by an injurious stimulus of peripheral neurons and resulting in release of neuropeptides which affect vascular permeability and help initiate proinflammatory and immune reactions at the site of injury."

The methods of the above-identified application are directed generally to the use of **chemodenervating** agents as anti-inflammatory agents. It is important to note that botulinum toxin, a chemodenervating agent, is specific for nerve cells. On information and belief, nerve cells are the only receptors or sites for the binding of the heavy chain of botulinum toxin. Hence, the inventive methods of reducing inflammation using botulinum toxin operate at the nerve level.

Second, following stimulation or injury to a nerve cell, the resultant inflammatory cascade proceeds through the involvement of mast cells and the release of pre-formed inflammatory mediators from mast cells that further propagate the neurogenic inflammatory cascade. Several references, identified by Dr. Borodic at the interview with the Examiner on May 17, 2004, are submitted herewith with the accompanying Information Disclosure Statement. For example, Monteforte *et al.* (2001) teach that mast

cells "are best known for their involvement in hypersensitivity, allergic and anaphylactic reactions [references omitted], but they are also implicated in angiogenesis [reference omitted] and in various inflammatory conditions such as parasitic infections [reference omitted] as well as neurogenic inflammation [reference omitted]." (Page 77; first paragraph). Also, "growing evidence has indicated a functional interdependence between nerve and MCs (mast cells)." (Page 77, paragraph 2). In addition, Dimitriadou *et al.* (1991), for example, teaches that "[m]ast cells are involved in allergic reactions, but may also participate in neurogenic inflammation." (Abstract). Finally, Coderre *et al.* teach that "neurogenic inflammation is thought to be produced by an 'axon reflex' mechanism..." and that "[t]he mast cell, an immunocompetent cell that contributes to various inflammatory responses, also contributes to neurogenic inflammation." (Page 48; column 2).

In view of the foregoing amendment and remarks, Applicant respectfully requests that the Examiner grant benefit of priority to U.S. Provisional Application Serial No. 60/097,846 and withdrawal of the outstanding written description rejection of claims 17-19 and 21-23 and to the extent it may be applied to new claims 24-29.

CONCLUSION

Applicant believes that the above-referenced application is in condition for allowance. Reconsideration and withdrawal of the outstanding rejections and early notice of allowance to that effect is respectfully requested.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 13-3250, reference No. 33677.00600. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F. R. § 1.136(a)(3).

If the Examiner finds that a telephone conference would further prosecution of this application, the Examiner is invited to contact the undersigned at 202-835-7553.

Respectfully submitted,

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